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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/544,045	04/06/2000	Brian Lee Sauer	OMRF 178	8128

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EXAMINER	
LAMBERTSON, DAVID A	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 01/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/544,045	SAUER ET AL.	
	Examin r	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cov r sheet with th correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 29 September 2003.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-49 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) 1-23 is/are allowed.

6)☒ Claim(s) 24-49 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Receipt is acknowledged of a reply to the previous FINAL Office Action, filed July 14, 2003. Furthermore, receipt is acknowledged of an Appeal Brief filed in response to the same previous FINAL Office Action.

Applicant is advised that the examination of the instant case has been transferred from the previous examiner, William Sandals, Ph.D. All correspondence should be directed to the new examiner, David A. Lambertson.

As a direct result of the re-docketing of the case, the issues set forth in the FINAL Office Action and Applicant's Response have been reconsidered despite the filing of an Appeal Brief. Concerning this matter, Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

Claims 1-49 are pending and under consideration in the instant application. Claims 50-65 were previous cancelled. Any rejection of record in the previous FINAL Office Action, mailed April 9, 2003, that is not addressed in this action has been withdrawn.

Because this Office Action raises new issues that were not previous addressed in the previous Office Action, this Office Action is Non-Final. Furthermore, as all rejections set forth in the previous Office Actions have been vacated (as it regards the grounds set forth in those Office Actions), Applicant's arguments are moot and will not be addressed on the rejection.

Information Disclosure Statement

The information disclosure statement filed February 15, 2001 has been considered, and a signed and initialed copy of the form PTO-1449 is attached to this Office Action. It is not immediately clear that this IDS has been considered on the record, either in the previous Office Actions or in the electronic file of the application. As such, the examiner apologizes if this is a duplication of a previous IDS, but it is necessary to make the record clear.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection that is not necessitated by amendment.**

Applicant claims the use of a mutant recombinase identified by the methods set forth in claims 1-23 of the instant application. The claims read on a broad genus of mutant recombinases that have not been described in the specification in such a manner that would allow the skilled artisan to envision the recombinases to be used in the methods of claims 24-49.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed genus. In the instant case, the specification does not sufficiently describe a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics.

Applicant claims the use of a mutant recombinase by function only (i.e., how it functions in an assay used to identify it), without any disclosed or known correlation between the elements and their function. The specification only provides teachings regarding a mutant Cre recombinase, specifically a Cre recombinase that has a mutation in a glutamine residue at amino acid position 262; the specification also describes additional mutations that exist in conjunction with this primary mutation. However, the definition of the term "recombinase" that is set forth in the instant specification (see for example page 13, lines 23-26) encompasses many more enzymes, including Int, Flp, resolvases, integrases, etc., which do not have a distinct or sufficient structure-function relationship with the Cre recombinase. The specification does not teach how to use mutant Int, Flp, resolvases or integrases that have altered site specificities because the specification does not describe these mutant recombinases in sufficient detail such that the skilled artisan can envision these mutant recombinases with altered site specificity. In other words, the skilled artisan cannot envision the corresponding mutations in these

enzymes that would result in the altered specificity described for the Cre recombinases based solely on the disclosure of the instant specification. Because the skilled artisan cannot envision a sufficient number of embodiments of the instant invention from the instant specification, the specification does not satisfy the written description requirement of 35 USC § 112, first paragraph.

The prior art does not provide sufficient information on the subject to overcome the deficiencies of the instant specification. There is no description in the prior art that allows one to envision a representative number of mutant recombinases with altered recombination site specificity by disclosing structural or functional features of recombinases so that one of skill in the art could envision the claimed invention. Thus the skilled artisan cannot rely on the prior art to envision a sufficient number of embodiments of the instant invention to see that the applicant was in possession of the claimed genus.

Although applicant is not directly claiming the recombinases identified in the methods of claims 1-23, a description of the identified recombinases is still required in order to practice the invention of claims 24-49. For illustrative purposes, the Int recombinase is provided as an example of how the written description requirement is deficient in the instant case. While the instant specification describes a method to *identify* an Int mutant that has altered recombination site specificity, the skilled artisan cannot actually *use* the mutant Int unless the skilled artisan can *envision* the mutant Int recombinase. Without a description of a structure-function relationship for a mutant Int recombinase, it is quite impossible to envision what this mutant recombinase would look like (i.e., where is the mutation(s) that result in the altered recombination site specificity).

The instant specification describes a particular mutant for the Cre recombinase; however, there is no way to correlate this mutation with a corresponding functional mutation in Int (or any other recombinase). Thus, the skilled artisan could not practice the methods of claims 24-49 along the broad scope that is claimed because the skilled artisan cannot envision the broad genus of mutant recombinases that must be used in the claimed invention. Therefore the instant specification does not satisfy the written description requirement to show the skilled artisan that they were in possession of the claimed genus.

Claims 24-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of a mutant *Cre recombinase* to produce site-specific recombination in a cell or *non-human* animal that is *genetically engineered to undergo site-specific recombination*, does not reasonably provide enablement for the use of any recombinase to produce recombination in a cell or human that has not been engineered to undergo site-specific recombination. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. **This is a new rejection that is not necessitated by amendment.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986)

and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), and the most relevant factors are indicated below:

Nature of the invention. The nature of the invention is a method of producing a site-specific recombination event in any cell or an animal. The invention makes use of a mutant recombinase that is identified by a method, wherein the mutant recombinase recognizes site-specific recombination sites that are not recognized by the wildtype/normal recombinase. It is important to recognize that the instant claims are commonly referred to as "reach-through" claims, where the claims reflect the use of an invention (in this case, a mutant recombinase) that is identified by a screening method. However, it must also be recognized that these "reach-through" claims are subject to the conditions of 35 USC § 112, first paragraph in that they must allow the skilled artisan to make and use the invention. Furthermore, it must be reiterated that the standard for meeting the enablement requirement involves the ability to "make and use" the invention, and that this standard is not equivalent to the ability to "identify" a component that is used in the invention.

As it regards the issue of "reach-through" claims, it is noted that the skilled artisan must be able to use the full scope of mutant recombinases that are set forth in the claims, and be able to use these recombinases in the full scope of cells/organisms that are set forth in the claims.

Scope of the invention. The scope of the invention is very broad with regard to two aspects of the claims: (1) the mutant recombinases that are used in the claims; and (2) the types of cells/organisms in which the recombinases are functional. With regard to (1), the invention is very broad because of the number of recombinases that are set forth to be

used in the claims. Applicant's definition includes *any* recombinase, resolvase, and integrase, such as Cre, Flp, Int, etc., although the instant specification only specifically describes a particular mutation in the Cre recombinase that causes altered site selection. While a large number of recombinases are known in the art, there is very little description of mutations in these enzymes that cause them to recognize different recombination sites, and there is little description of an ability to correlate a structure-function relationship between each of these enzymes. As it regards (2), the claims read on the ability to perform recombination in virtually any cell or organism, even those that are not genetically engineered to contain a site that is recognized by the mutant recombinase used in the method. The scope here is very broad because the skilled artisan cannot reasonably be apprised of what cells or organisms can be used in the method because the skilled artisan cannot know which organisms inherently contain a recognized site-specific recombination site. Since it is not possible to genetically engineer a human being to contain such recombination sites, the cells/organisms must also be non-human.

State of the art. The state of the art appears silent with regard to mutant recombinases that have altered site specificities (it is impossible to ascertain if a mutant recombinase that is well-known in the art will have altered site-specificity until it is actually tested on variant recombination sites). However, the art is also silent with regard to the ability to translate a mutation in one recombinase to a mutation in an entirely different recombinase in a manner such that the function of the mutation in the first recombinase is transferred to the second recombinase. In other words, the skilled artisan would be unable to make just any mutant recombinase having altered site specificity without explicit instruction on how to do so (i.e., where you can/must make the mutation), or without a clear description

of a mutation in a representative number of recombinases that shows a structure-function relationship (i.e., in five distinct recombinases, a corresponding mutation results in the same altered functionality). This is similar to the rejection set forth above with regard to written description, and encompasses each of the issues as described therein.

Number of working examples and Guidance provided by applicant. The instant specification only provides guidance with respect to mutations in the Cre recombinase that have altered site specificity. There is no guidance in the specification that indicates how to translate the mutations at amino acid position 262 in Cre to a corresponding mutation in Int, Flp, or any other recombinase, wherein the mutation results in altered site specificity for these recombinases. This is also similar to the rejection set forth above with regard to written description, and encompasses each of the issues as described therein.

Unpredictability of the art and Amount of experimentation required. The invention as claimed is highly unpredictable with regard to the broad scope in which the claims are set forth. Because of this unpredictability, an undue amount of trial and error experimentation would be required to practice the claimed invention.

The first area of unpredictability resides in the recombinase that is to be used in the invention. The claimed invention involves the use of *any* recombinase identified by a particular method, while the specification only describes one type of mutant recombinase as identified by the same method. However, Applicant's definition of "recombinase" includes any recombinase, many of which are structurally distinct form the sole example set forth in the instant specification, which is a Cre recombinase having a mutation at amino acid position 262. There is no way to correlate this single mutation into Int, Flp,

or any of the other recombinases encompassed by Applicant's definition, in such a manner that the site-specificity of the recombinase is significantly altered. Thus, in order to determine which recombinase to use in the invention, the skilled artisan would have to identify the mutations in each recombinase that result in an altered site-specificity. This involves a great deal of empirical trial and error experimentation that is unpredictable and undue because there is no way to even guess which mutations would correspond to an altered site selection based simply on the teachings of the instant application and the prior art. Again, the ability to "make and use" is not commensurate with the ability to "identify."

The second area of unpredictability regards the type of cell or organism in which recombination can be produced using the mutant recombinase. Without an indication that the cell or organism has been genetically engineered to contain the site that is now recognized by the mutant recombinase, the skilled artisan can have no way of knowing which cells are amenable to this recombination event. In order to do so, the skilled artisan would have to practice undue and unpredictable trial and error experimentation by randomly testing a cell or organism for the ability to undergo recombination in the presence of the mutant recombinase; furthermore, in many of these instances, it would be impossible to accurately tell if a recombination event actually occurred. Thus, the skilled artisan could not reasonably practice the invention in any cell or organism, absent a clear indication that the cell or organism (non-human, since there is no genetic manipulation of humans) has been genetically engineered to contain a recognized recombination sequence.

In conclusion, claims 24-49 are enabled for producing recombination in a cell or non-human organism that is genetically engineered to undergo site-specific recombination by using a mutant Cre recombinase, but are not enabled for the use of *any* mutant recombinase in *any* cell. There is a great deal of trial and error experimentation involved in practicing the full scope of the invention because the broad scope of mutant recombinases that can be used in the invention is completely unknown to the skilled artisan, as are the broad number of cells and organisms which can undergo recombination in the absence of genetic engineering of the cells/organisms to contain the recognized sites. The skilled artisan would have to empirically determine the mutant recombinases that can be used in the invention, what sites these recombinases now recognize (for each individual recombinase), and in what cells and organisms each of these newly recognized sites resides. This is clearly an undue and unpredictable amount of experimentation. Therefore, the claimed invention is not enabled for the broad scope of the invention set forth in the claims.

Allowable Subject Matter

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson, Ph.D.
AU 1636

JAMES KETTER
PRIMARY EXAMINER